(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 992 244 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
**12.04.2000 Bulletin 2000/15**

(21) Application number: **98929748.6**

(22) Date of filing: **30.06.1998**

(51) Int. Cl.[7]: **A61K 47/30**

(86) International application number:
**PCT/JP98/02916**

(87) International publication number:
**WO 99/01156 (14.01.1999 Gazette 1999/02)**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE**

(30) Priority: **02.07.1997 JP 17682397**

(71) Applicant:
**SANTEN PHARMACEUTICAL CO., LTD.**
**Higashiyodogawa-ku, Osaka-shi, Osaka 533-8651 (JP)**

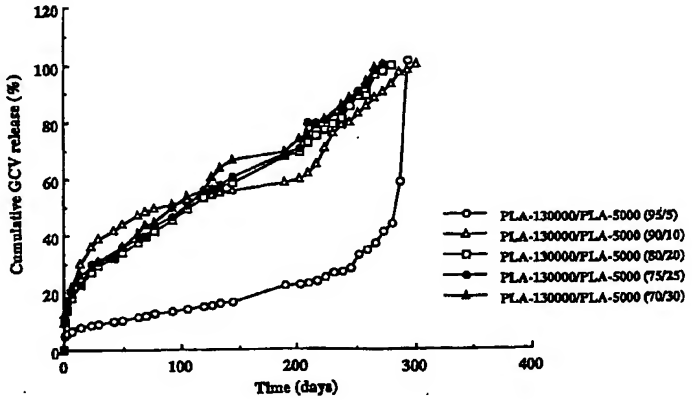
(72) Inventors:
- **OGURA, Yuichiro**
  **Nagoya-shi, Aichi 466-0826 (JP)**
- **KUNOU, Noriyuki**
  **Yawata-shi, Kyoto 614-8372 (JP)**
- **OTA, Atsutoshi**
  **Osaka-shi, Osaka 536-0001 (JP)**

(74) Representative:
**Peaucelle, Chantal**
**Cabinet Armengaud Aine**
**3, avenue Bugeaud**
**75116 Paris (FR)**

# (54) POLYLACTIC ACID SCLERAL PLUGS

(57) The present invention provides a scleral plug which can release a drug accurately in a specified amount to the end. The scleral plug according to the present invention is formed from a blend of a high-molecular weight polylactic acid having a molecular weight of 40,000 or higher and a low-molecular weight polylactic acid having a molecular weight of 40,000 or lower and contains a drug for treatment or prevention of a vitreoretinal disease. A blending ratio of the high-molecular weight polylactic acid and the low-molecular weight polylactic acid is preferably 90/10 to 50/50, more preferably 90/10 to 70/30, most preferably 80/20. The molecular weight of the high-molecular weight polylactic acid is preferably 40,000 to 200,000. The molecular weight of the low-molecular weight polylactic acid is preferably 3,000 to 40,000, more preferably 5,000 to 20,000. The drug is, for example, an antiulcer agent, an antiviral agent, an anti-inflammatory agent, an antifungal agent or an antimicrobial.

Fig.1




EP 0 992 244 A1

## Description

### Technical Field

**[0001]** The present invention relates to a scleral plug made from a novel composition with a view to treating or preventing vitreoretinal disorders.

### Background Art

**[0002]** Intraocular diseases such as diseases of a retina or vitreous body are often intractable, and a development of an effective treatment method is eagerly desired. Though ocular diseases are most generally treated by instillation of drugs, the drugs are hardly delivered to the intraocular tissues such as a retina and vitreous body, rendering the treatment of the intraocular diseases all the more difficult. An attempt was made to treat the diseases by intravenous administration or the like. However, because of a blood-aqueous barrier, it is difficult to allow the drug to be delivered to attain an effective concentration. A method is known in which the drug is directly injected into the vitreous body. However, injection of a high concentration drug all at once causes damage to intraocular tissues and, moreover, it is not practical to repeat the injection because of the danger of infection and the cumbersomeness of treatment procedure.

**[0003]** In view of this, a scleral plug made of a biodegradable copolymer was devised (See United States Patent No. 5,707,643). The scleral plug can be easily inserted into a small incision of sclera that is formed at the time of a vitreoretinal surgery. This scleral plug is formed from a poly(lactide-co-glycolide) made of lactic acid units and glycolic acid units, containing a drug, whereby the drug is gradually released into a vitreous body by utilizing the biodegradation of the copolymer in order to treat the vitreoretinal diseases.

**[0004]** The scleral plug is inserted into the small scleral incision formed at the time of the vitreoretinal surgery. The scleral plug needs to be strong enough not to break or chip by manipulation with tweezers during surgery. Moreover, the scleral plug needs to have properties to release a drug gradually during the desired period of time for treatment and to be degraded in ocular tissues and absorbed in the tissues afterwards. United States Patent No. 5,707,643 discloses that the scleral plug is preferred to have a molecular weight (weight-average) of the copolymer of 10,000 to 1,000,000 and proposes that lactic acid and glycolic acid are used in an appropriate copolymerization ratio making the most of both characteristics. However, there was still room for improvement in the scleral plug made from the poly(lactide-co-glycolide) in terms of the sustained drug release. Namely, when the drug is required to be gradually released over a long period of time, a hydrolysis rate of the plug is designed to be slow. Accordingly, the resulting oligomers and monomers owing to the hydrolysis are not released out of matrix smoothly, and they are gradually accumulating in the matrix. Consequently, it is feared that the inner osmotic pressure increases gradually and the drug is released at a time accompanied by disintegration of the plug. Accordingly, it is not easy to release the drug accurately in a constant amount to the end, and improvement of the plug was required.

### Disclosure of the Invention

**[0005]** As a result of precise studies of improvement of this scleral plug) the present inventors found that the above-mentioned problem can be solved by combining a high-molecular weight polylactic acid with a low-molecular weight polylactic acid in a suitable ratio and blending them.

**[0006]** The scleral plug is characterized by being formed from a blend of the high-molecular weight polylactic acid and the low-molecular weight polylactic acid. First, the low-molecular weight polylactic acid, which is apt to be hydrolyzed, degrades in vivo gradually and begins to release a drug gradually, and the whole plug changes into porous structure gradually. Next, the high-molecular weight polylactic acid, which is hardly hydrolyzed, degrades gradually. The release of the drug can be controlled to be constant until the plug disintegrates, since the resulting oligomers and monomers owing to hydrolysis are smoothly released through the porous structure out of matrix.

**[0007]** The high-molecular weight polylactic acid means polylactic acid having a molecular weight (weight-average, the same definition is applied hereinafter) of 40,000 or higher. The low-molecular weight polylactic acid means polylactic acid having a molecular weight of 40,000 or lower. However, polylactic acid having a molecular weight of 40,000 is not used as the high-molecular weight polylactic acid and the low-molecular weight polylactic acid at the same time. It is not particularly necessary to define the upper limit of the molecular weight of the high-molecular weight polylactic acid, but the molecular weight is practically 1,000,000 or lower, considering a releasing period of the drug, that is, a degradation rate of the plug. The lower limit of the molecular weight of the low-molecular weight polylactic acid is not also particularly limited, but the molecular weight is practically 3,000 or higher, considering a releasing rate of the drug. The release of the drug can be controlled by appropriately selecting each molecular weight of the high-molecular weight polylactic acid and the low-molecular weight polylactic acid used, and a blending ratio thereof.

**[0008]** When it is necessary to release the drug over a long period of time, the scleral plug of the present invention is particularly suitably used. The releasing period can be determined mainly on the basis of the molecular weight of the high-molecular weight polylactic acid used. For example, when a high-molecular weight

polylactic acid having a molecular weight of 100,000 to 200,000 is used as a major component, the releasing period can be adjusted to about half a year to one year. When a high-molecular weight polylactic acid having a molecular weight of 40,000 to 100,000 is used as a major component, the releasing period can be adjusted to about several weeks to half a year. When a high-molecular weight polylactic acid having a molecular weight of 200,000 or higher is used, the plug can have longer-term releasing persistence. The molecular weight of the high-molecular weight polylactic acid is selected considering a possible content and an effective concentration of the drug.

**[0009]** A main role of the low-molecular weight polylactic acid is to make the plug porous and to control the release amount of the drug to be constant. This effect depends on mainly a blending ratio of the low-molecular weight polylactic acid. When the blending ratio of the low-molecular weight polylactic acid is too high, an initial releasing rate of the drug is high, and it is difficult to keep the release of the drug constant over a long period of time. On the contrary when the blending ratio is too low, it is feared that the porous structure is not formed well, the resulting oligomers and the monomers owing to the hydrolysis are not released smoothly, the plug decomposes at a time in a final stage of the release of the drug, and the drug is also released at a time. Accordingly, the blending ratio of the high-molecular weight polylactic acid and the low-molecular weight polylactic acid is usually about 90/10 to about 50/50, preferably about 90/10 to about 70/30, most preferably about 80/20.

**[0010]** The releasing period of the drug and an amount of the drug to be released are basically controlled to be constant by the molecular weight of the high-molecular weight polylactic acid and the blending ratio of the low-molecular weight polylactic acid. However, the releasing period of the drug depends on the molecular weight of the low-molecular weight polylactic acid, too. When the molecular weight of the low-molecular weight polylactic acid is decreased, the releasing rate of the drug becomes a little high. On the contrary, when the molecular weight is increased, the releasing rate of the drug becomes a little low. Accordingly, the molecular weight of the low-molecular weight polylactic acid adjusts the releasing period finely. The molecular weight of the low-molecular weight polylactic acid can appropriately be changed depending on the desired releasing period. The molecular weight is selected usually in the range of 3,000 to 40,000, more preferably in the range of 5,000 to 20,000.

**[0011]** As regards physical strength, which is a requirement of the scleral plug, the molecular weight of the polymer can be 10,000 or higher. When the high-molecular weight polylactic acid having the molecular weight of 40,000 or higher is used as a major component like the present invention, the scleral plug maintains sufficient strength.

**[0012]** The polylactic acid can be a DL-, L- or D-form, and it is preferable to use the DL- or L-form.

**[0013]** The scleral plug can have essentially the same shape and size as those disclosed in United States Patent No. 5,707,643, that is, a nail-like shape comprising a head portion and a shaft portion. The end of the shaft portion can be formed in an acute-angled shape.

**[0014]** The scleral plug is used for treatment or prevention of various vitreoretinal diseases. Examples of specific diseases are viral or bacterial infectious, proliferative vitreoretinopathy accompanied by proliferation of new blood vessels or retinal cells, retinal hemorrhage, retinal detachment or retinoblastoma due to various causes or the like. The drug to be contained in the scleral plug is not limited and can be selected depending on the diseases. For example, for treatment of viral infectious, antiviral agents such as ganciclovir are used. Doxorubicin hydrochloride, etc. are used for treating proliferative vitreoretinopathy. Content of the drug can appropriately be adjusted depending on the kinds, the necessary effective concentrations and the releasing periods of the drug, symptoms, etc. For example, the content of ganciclovir is usually 1 to 4 mg, preferably 1.5 to 2.5 mg. The weight of the scleral plug of the present invention is about 8 to 10 mg, and the drug content is determined considering balance of a sustained release effect and an amount required for the treatment.

**[0015]** A plurality of the scleral plugs of the present invention can be used simultaneously. When the scleral plug becomes unable to maintain the effective concentration of the drug, it can be replaced with a new one.

**[0016]** Particular techniques are not required for producing the scleral plug of the present invention. For example, the scleral plug is obtained by dissolving the high-molecular weight polylactic acid, the low-molecular weight polylactic acid and the drug in a certain amount of a solvent such as acetic acid, lyophilizing the solution and then forming plugs out of the obtained powder.

Brief Description of Drawings

**[0017]**

Figure 1 is a graph showing relations between cumulative released amounts (%) of ganciclovir (GCV) from a scleral plug formed from a blend comprising high-molecular weight polylactic acid having molecular weight of 130,000 (PLA-130000) and low-molecular weight polylactic acid having molecular weight of 5,000 (PLA-5000) in a specific ratio, and a period of time (days) (average value of five samples (n=5)).

Figure 2 is a graph showing relations between cumulative released amounts (%) of gavciclovir (GCV) from a scleral plug formed from a blend comprising high-molecular weight polylactic acid having molecular weight of 130,000 (PLA-130000) and

low-molecular weight polylactic acid having molecular weight of 10,000 (PLA-10000) in a specific ratio, and a period of time (days) (average value of five samples (n=5)).

Figure 3 is a graph showing relations between cumulative released amounts (%) of ganciclovir (GCV) from a scleral plug formed from a blend comprising high-molecular weight polylactic acid having molecular weight of 130,000 (PLA-130000) and low-molecular weight polylactic acid having molecular weight of 20,000 (PLA-20000) in a specific ratio, and a period of time (days) (average value of five samples (n=5)).

Figure 4 is a graph showing relations between cumulative released amounts (%) of ganciclovir (GCV) from a scleral plug formed from a blend comprising high-molecular weight polylactic acid having molecular weight of 130,000 (PLA-130000) and low-molecular weight polylactic acid having molecular weight of 40,000 (PLA-40000) in a specific ratio, and a period of time (days) (average value of five samples) (n=5).

Figure 5 is a graph showing relations between cumulative released amounts (%) of ganciclovir (GCV) from a scleral plug formed from a blend comprising high-molecular weight polylactic add having molecular weight of 70,000 (PLA-70000) and low-molecular weight polylactic acid having molecular weight of 5,000 (PLA-5000) in a specific ratio, and a period of time (days) (average value of five samples (n=5)).

Figure 6 is a graph showing relations between cumulative released amounts (%) of ganciclovir (GCV) from a scleral plug formed from a blend comprising high-molecular weight polylactic acid having molecular weight of 70,000 (PLA-70000) and low-molecular weight polylactic acid having molecular weight of 10,000 (PLA-10000) in a specific ratio, and a period of time (days) (average value of five samples (n=5)).

Figure 7 is a graph showing relations between cumulative released amounts (%) of ganciclovir (GCV) from a scleral plug formed from a blend comprising high-molecular weight polylactic acid having molecular weight of 70,000 (PLA-70000) and low-molecular weight polylactic acid having molecular weight of 20,000 (PLA-20000) in a specific ratio, and a period of time (days) (average value of five samples (n=5)).

Figure 8 is a graph showing relations between cumulative released amounts (%) of ganciclovir (GCV) from a scleral plug formed from a blend comprising high-molecular weight polylactic acid having molecular weight of 40,000 (PLA-40000) and low-molecular weight polylactic acid having molecular weight of 5,000 (PLA-5000) in a specific ratio, and a period of time (days) (average value of five samples (n=5)).

Best Mode for Carrying out the Invention

**[0018]** Examples are shown below. These Examples are intended for better understanding the present invention but are not to limit the scope of the present invention.

Example 1 (Production of scleral plug)

**[0019]** In acetic acid (10 ml) were dissolved a high-molecular weight polylactic acid having a molecular weight of 130,000 (800 mg), a low-molecular weight polylactic acid having a molecular weight of 5,000 (200 mg) and ganciclovir (250 mg). The obtained solution was lyophilized to give fine particle powder. A portion of the fine particle powder was placed on a hot plate to form the desired scleral plug. Ganciclovir content per a piece of the obtained scleral plug (about 1 mg) is about 2 mg.

**[0020]** By methods similar to Example 1 is obtained a scleral plug in which molecular weight of high-molecular weight polylactic acid is 130,000, 70,000 or 40,000, molecular weight of low-molecular weight polylactic acid is 3,000, 5,000, 10,000, 20,000 or 40,000 and a ratio of the high-molecular weight polylactic acid/the low-molecular weight polylactic acid is 90/10, 85/25, 80/20, 75/25, 70/30, 60/40 or 50/50. A scleral plug having ganciclovir content of about 1 mg, about 2 mg, about 3 mg or about 4 mg per a piece of the scleral plug is obtained.

Example 2 (Release test)

**[0021]** The scleral plug produced in Example 1 was shaken in a phosphate buffered solution (0.1 M, pH 7.4) to release a drug (ganciclovir). The release medium was collected at predetermined intervals and replaced with a new buffet These operations were repeated. Absorbance of the release medium at 254 nm was measured with a spectrophotometer, and an amount of the released drug was determined. Examples of the measurement results are shown in Figs. 1 to 8. It was confirmed that the drug (ganciclovir) does not decompose during the release test.

**[0022]** The results shown in Figs. 1 to 8 teach the followings.

1. Regarding change in blending ratio of high-molecular weight polylactic acid (HPLA) and low-molecular weight polylactic acid (LPLA)

**[0023]**

1) When the blending ratio of HPLA and LPLA is 95/5, the drug is rapidly released at a latter stage of the drug release, and an amount of the released drug is not kept constant from an initial stage to the final stage of the drug release. Namely, the released amount and a period of time do not have a

linear relation.

2) When the blending ratio of HPLA and LPLA is 95/10 to 50/50, rapid releases of the drug hardly take place even at the latter stage of the drug release. A releasing rate of the drug is a little high at the initial stage of the drug release, but the released amount is kept almost constant from a middle stage to the final stage of the drug release. In particular, when the blending ratio is 80/20, the released amount and the period of time have an almost linear relation.

2. Regarding effect of molecular weight of HPLA

**[0024]** Comparing scleral plugs having a constant blending ratio of HPLA and LPLA and constant molecular weight of LPLA, the drug releasing period becomes longer with increasing the molecular weight of HPLA. For example, comparing Fig. 1 with Fig. 5, when the molecular weight of HPLA is 130,000, the releasing period is about 300 days. When the molecular weight is 70,000, the releasing period is about 200 days.

3. Regarding effect of molecular weight of LPLA

**[0025]** Comparing scleral plugs having the constant blending ratio of HPLA and LPLA and constant molecular weight of HPLA, as the molecular weight of LPLA increases, the drug releasing period becomes a little long. For example, comparing Fig. 1 with Fig. 4, when the molecular weight of LPLA is 5,000, the releasing period is about 300 days. When the molecular weight is 40,000, the releasing period is about 350 to 400 days.

Industrial Applicability

**[0026]** The present invention relates to a scleral plug made from a novel composition with a view to treating or preventing a retina vitreoretinal disorders.

**Claims**

1. A scleral plug formed from a blend of a high-molecular weight polylactic acid having a molecular weight of 40,000 or higher and a low-molecular weight polylactic acid having a molecular weight of 40,000 or lower and containing a drug for treatment or prevention of a vitreoretinal disease.

2. The scleral plug according to claim 1, wherein a blending ratio of the high-molecular weight polylactic acid and the low-molecular weight polylactic acid is 90/10 to 50/50.

3. The scleral plug according to claim 1, wherein a blending ratio of the high-molecular weight polylactic acid and the low-molecular weight polylactic acid is 90/10 to 70/30.

4. The scleral plug according to claim 1, wherein a blending ratio of the high-molecular weight polylactic acid and the low-molecular weight polylactic acid is 80/20.

5. The scleral plug according to claim 1, wherein the molecular weight of the high-molecular weight polylactic acid is 40,000 to 200,000.

6. The scleral plug according to claim 1, wherein the molecular weight of the low-molecular weight polylactic acid is 3,000 to 40,000.

7. The scleral plug according to claim 1, wherein the molecular weight of the low-molecular weight polylactic acid is 5,000 to 20,000.

8. The scleral plug according to claim 1, wherein the drug is an antiulcer agent, an antiviral agent, an anti-inflammatory agent, an antifungal agent or an antimicrobial.

9. A scleral plug formed from a blend wherein a high-molecular weight polylactic acid having a molecular weight of 40,000 to 200,000 and a low-molecular weight polylactic acid having a molecular weight of 3,000 to 40,000 are blended in a blending ratio of 90/10 to 50/50 and containing a drug for treatment or prevention of a vitreoretinal disorder, a shape thereof being a nail-like shape having a head portion and a shaft portion, and the end of the shaft portion being formed in an acute-angled shape.

Fig.1

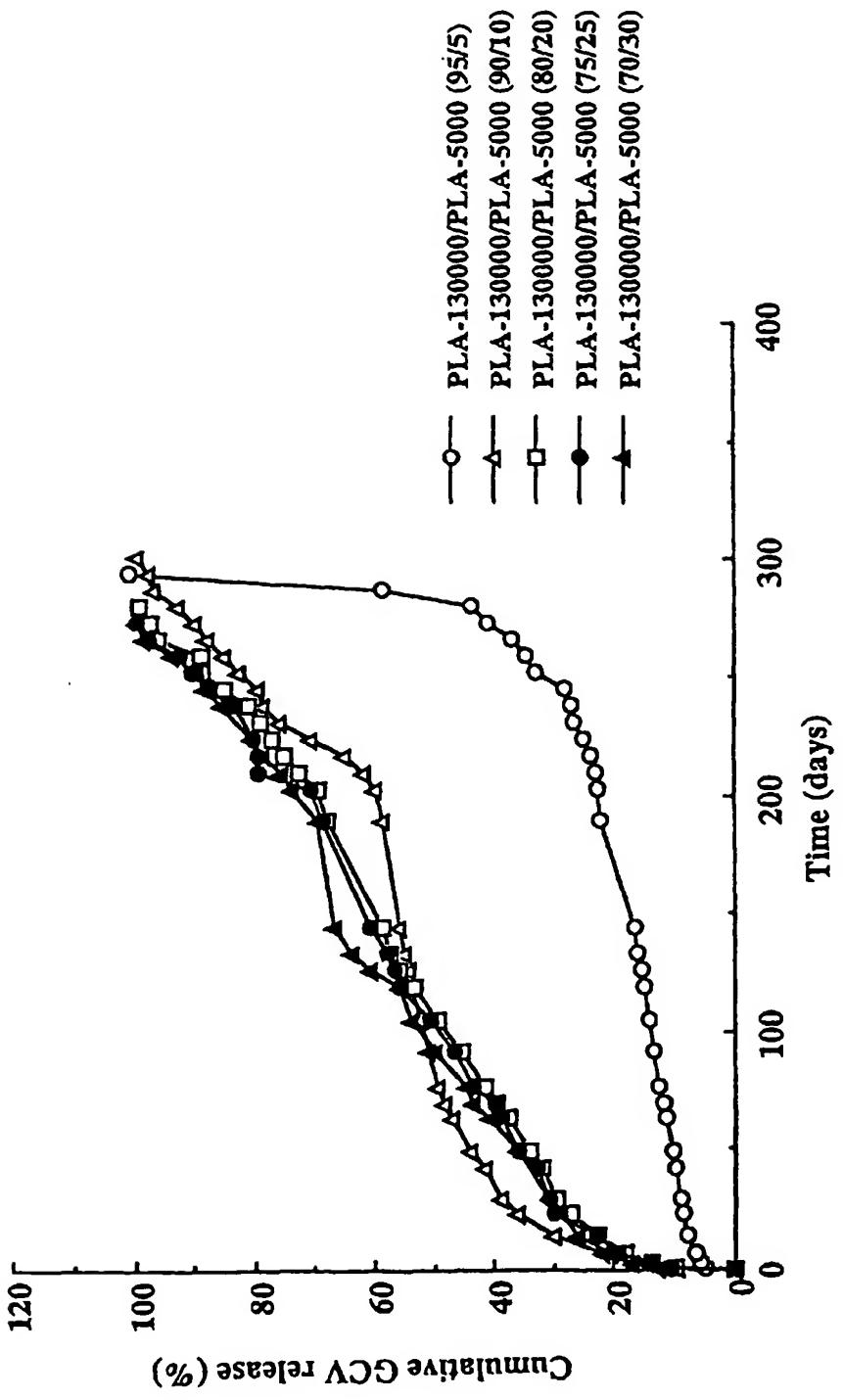

PLA-130000/PLA-5000 (95/5)
PLA-130000/PLA-5000 (90/10)
PLA-130000/PLA-5000 (80/20)
PLA-130000/PLA-5000 (75/25)
PLA-130000/PLA-5000 (70/30)
Cumulative GCV release (%)
120
100
80
60
40
20
0
0
100
200
300
400
Time (days)

Fig.2

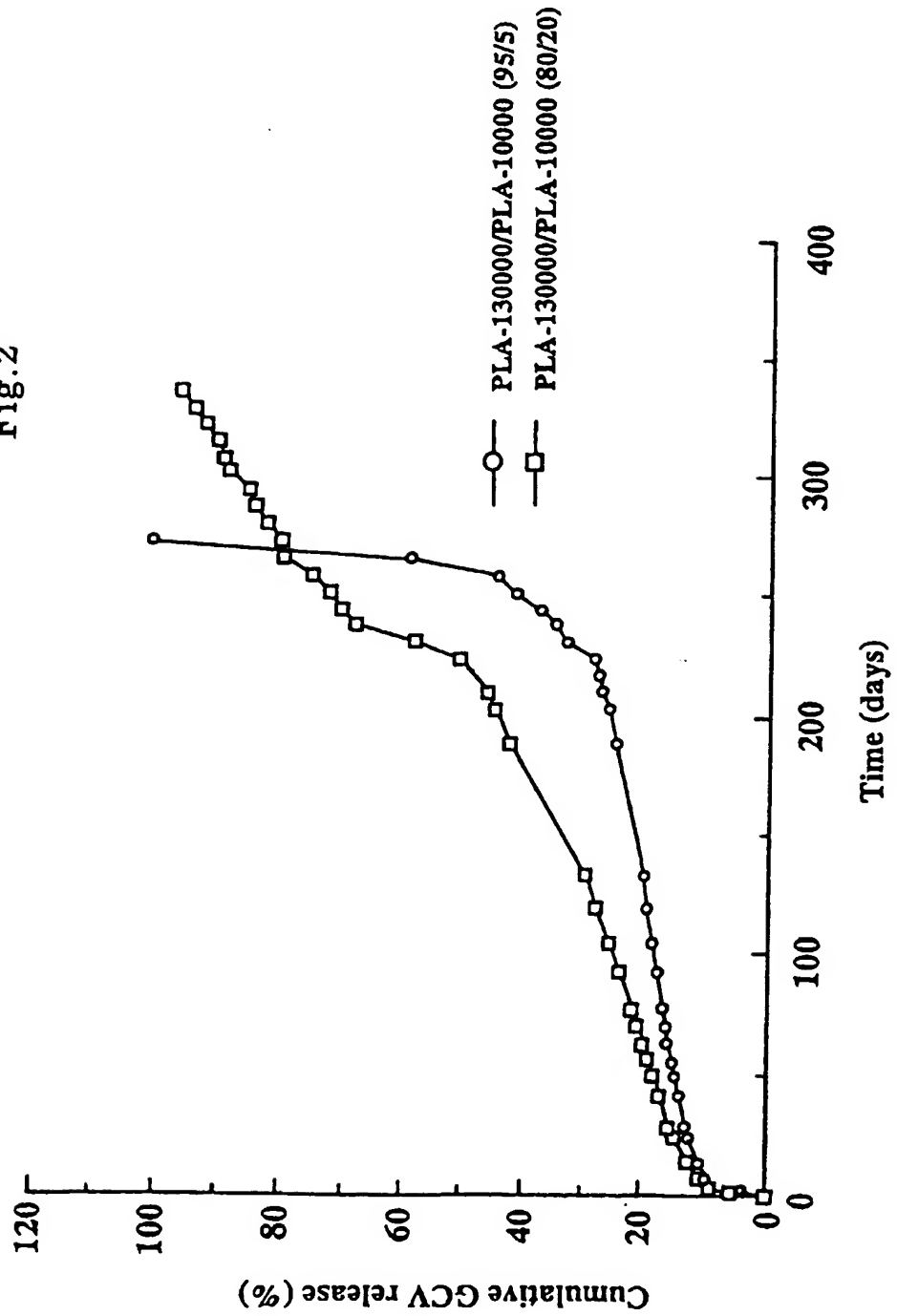
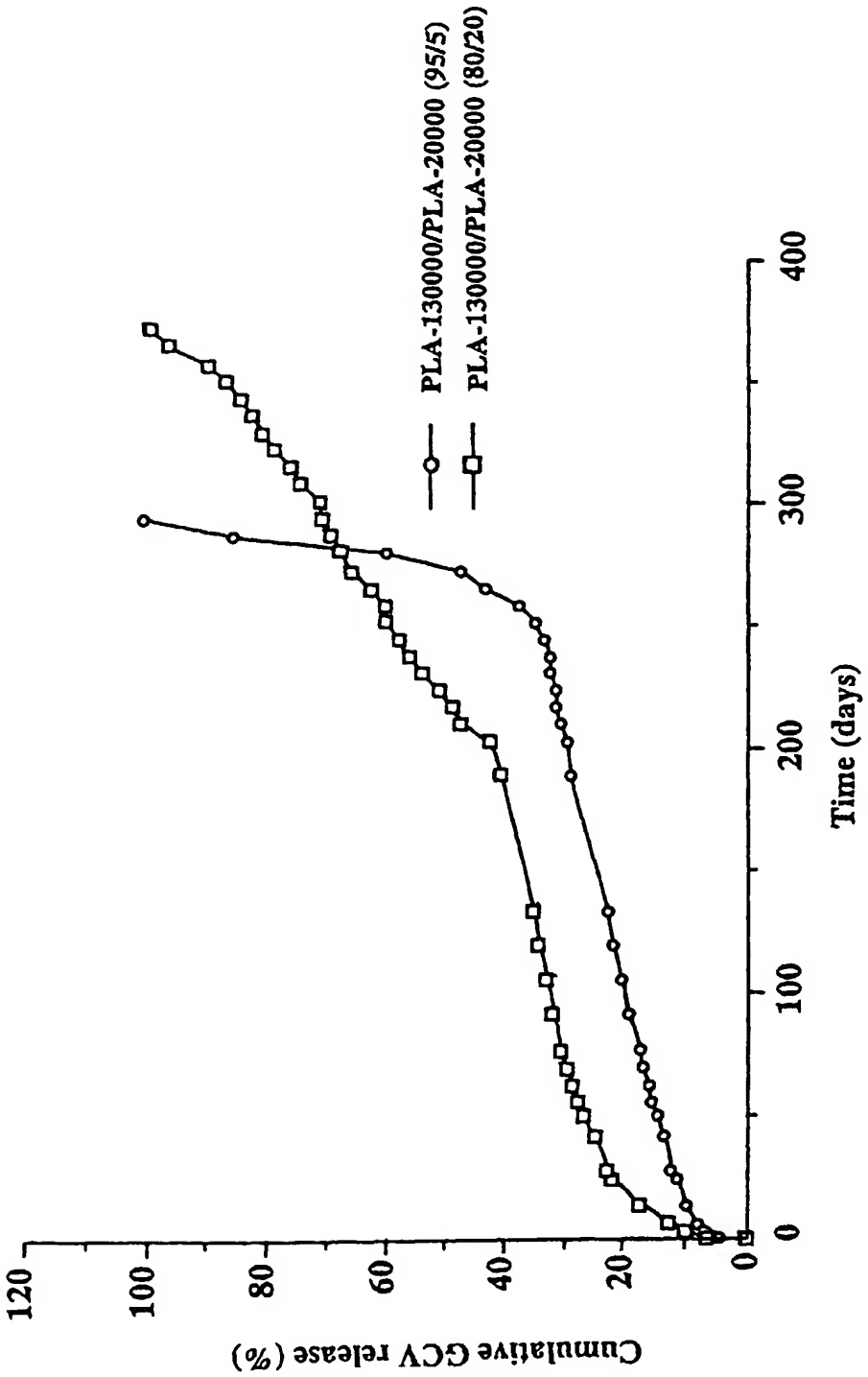

PLA-130000/PLA-10000 (95/5)
PLA-130000/PLA-10000 (80/20)
Cumulative GCV release (%)
Time (days)
0
20
40
60
80
100
120
0
100
200
300
400

Fig.3


Cumulative GCV release (%)
120
100
80
60
40
20
0
0
100
200
300
400
Time (days)
PLA-130000/PLA-20000 (95/5)
PLA-130000/PLA-20000 (80/20)

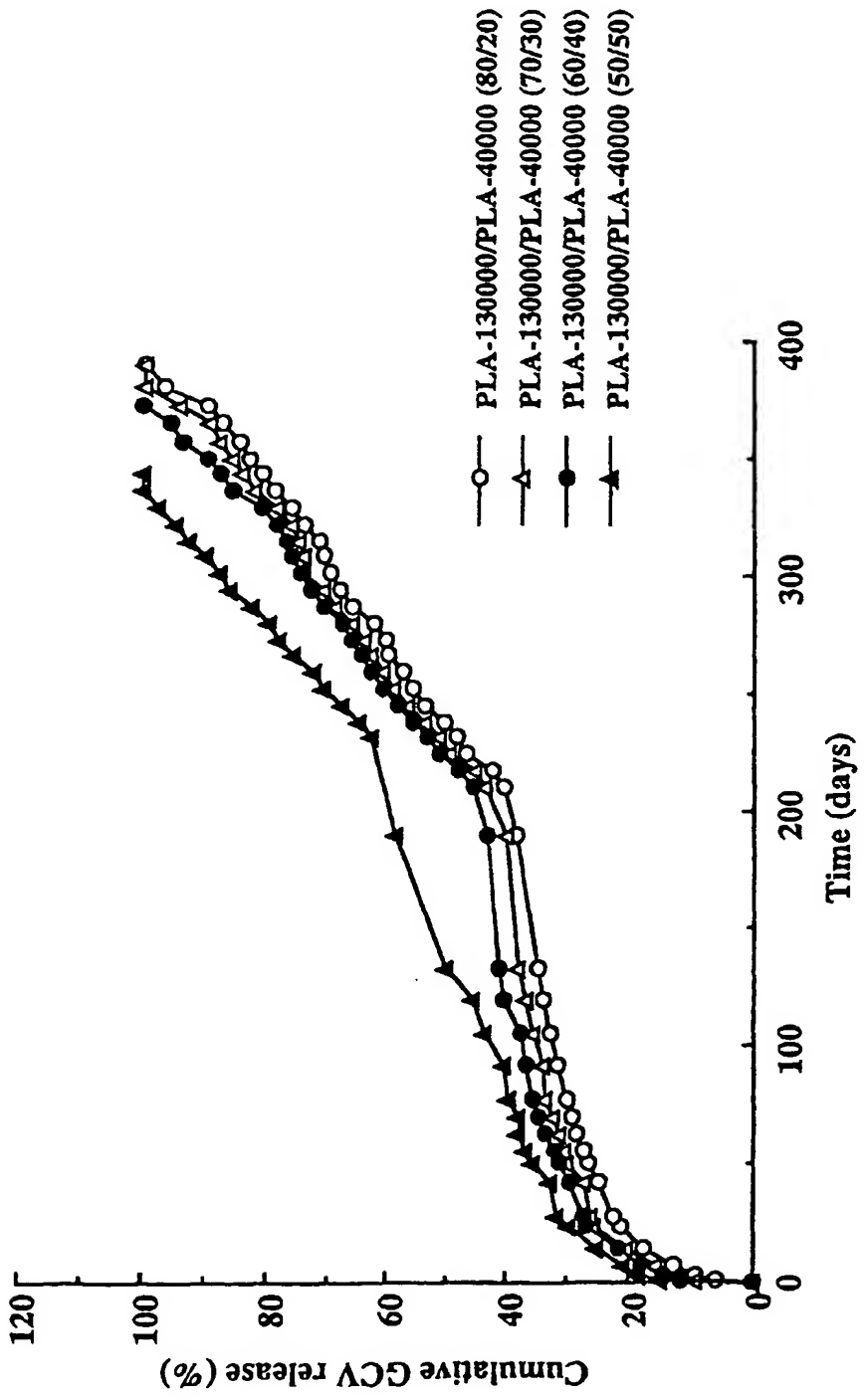

PLA-130000/PLA-40000 (80/20)
PLA-130000/PLA-40000 (70/30)
PLA-130000/PLA-40000 (60/40)
PLA-130000/PLA-40000 (50/50)
Cumulative GCV release (%)
120
100
80
60
40
20
0
0
100
200
300
400
Time (days)

Fig.4

Fig.5

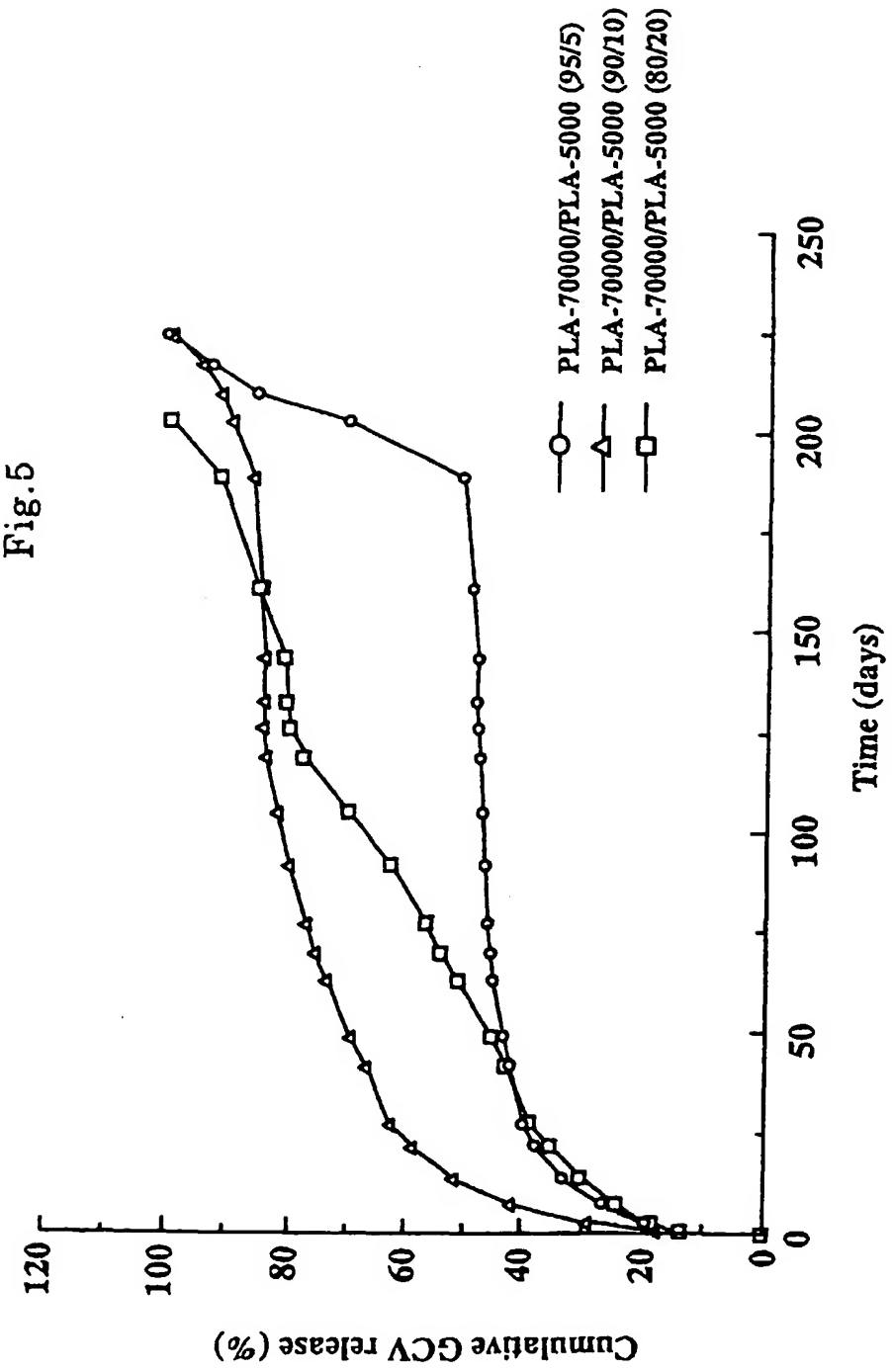

Cumulative GCV release (%)
120
100
80
60
40
20
0
0
50
100
150
200
250
Time (days)
PLA-70000/PLA-5000 (95/5)
PLA-70000/PLA-5000 (90/10)
PLA-70000/PLA-5000 (80/20)

Fig.6

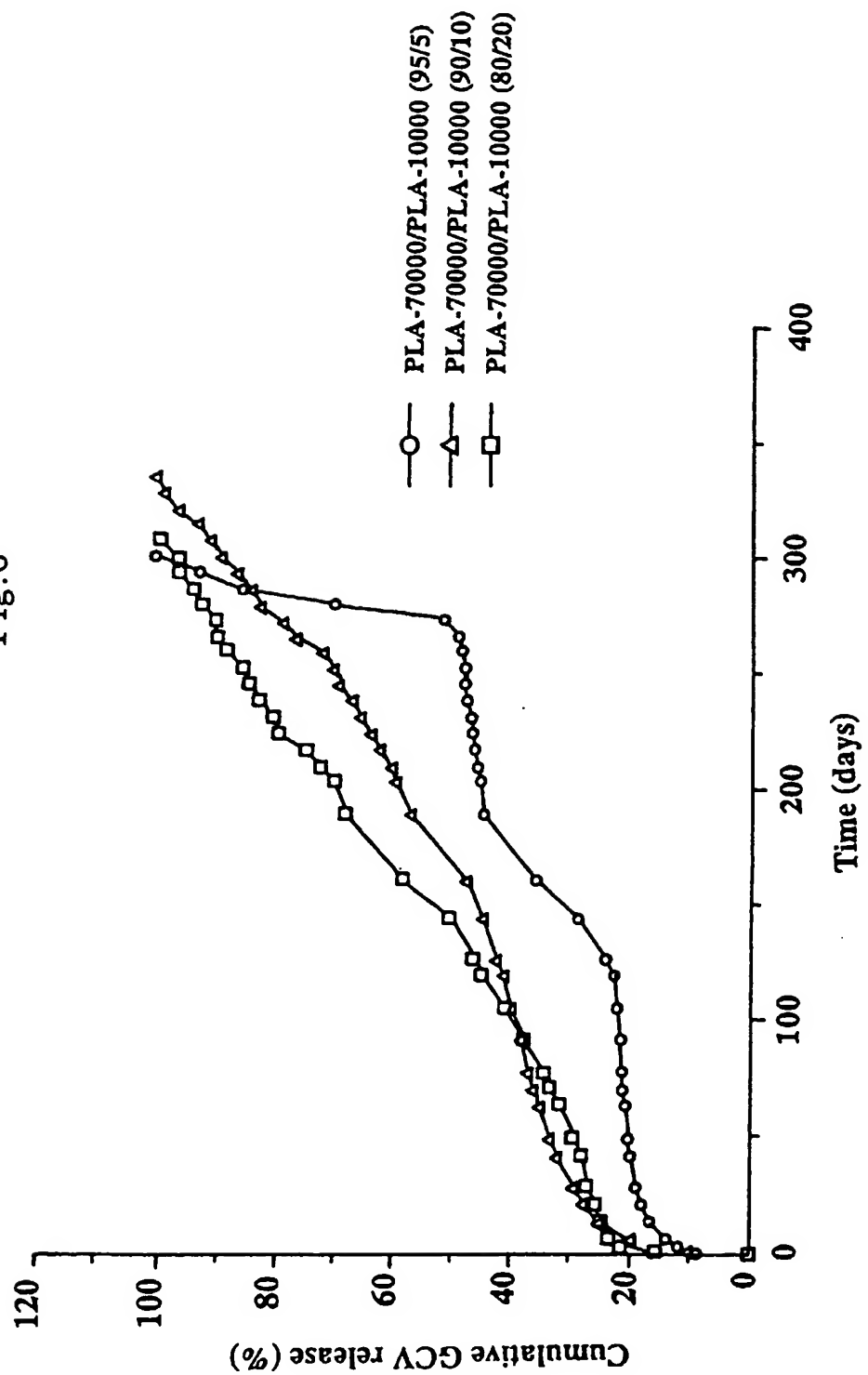

PLA-70000/PLA-10000 (95/5)
PLA-70000/PLA-10000 (90/10)
PLA-70000/PLA-10000 (80/20)
Cumulative GCV release (%)
Time (days)
0
20
40
60
80
100
120
0
100
200
300
400

Fig.7

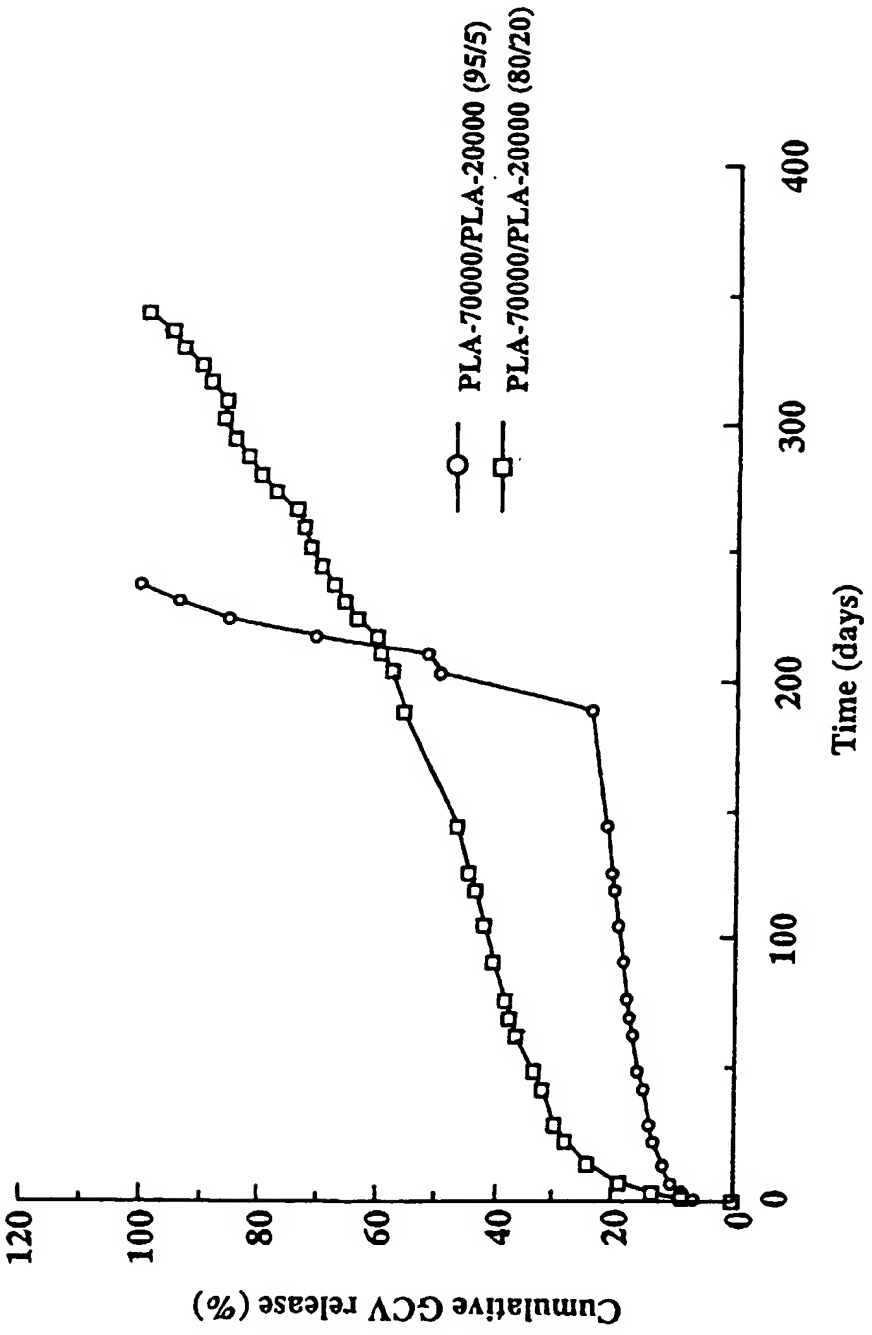
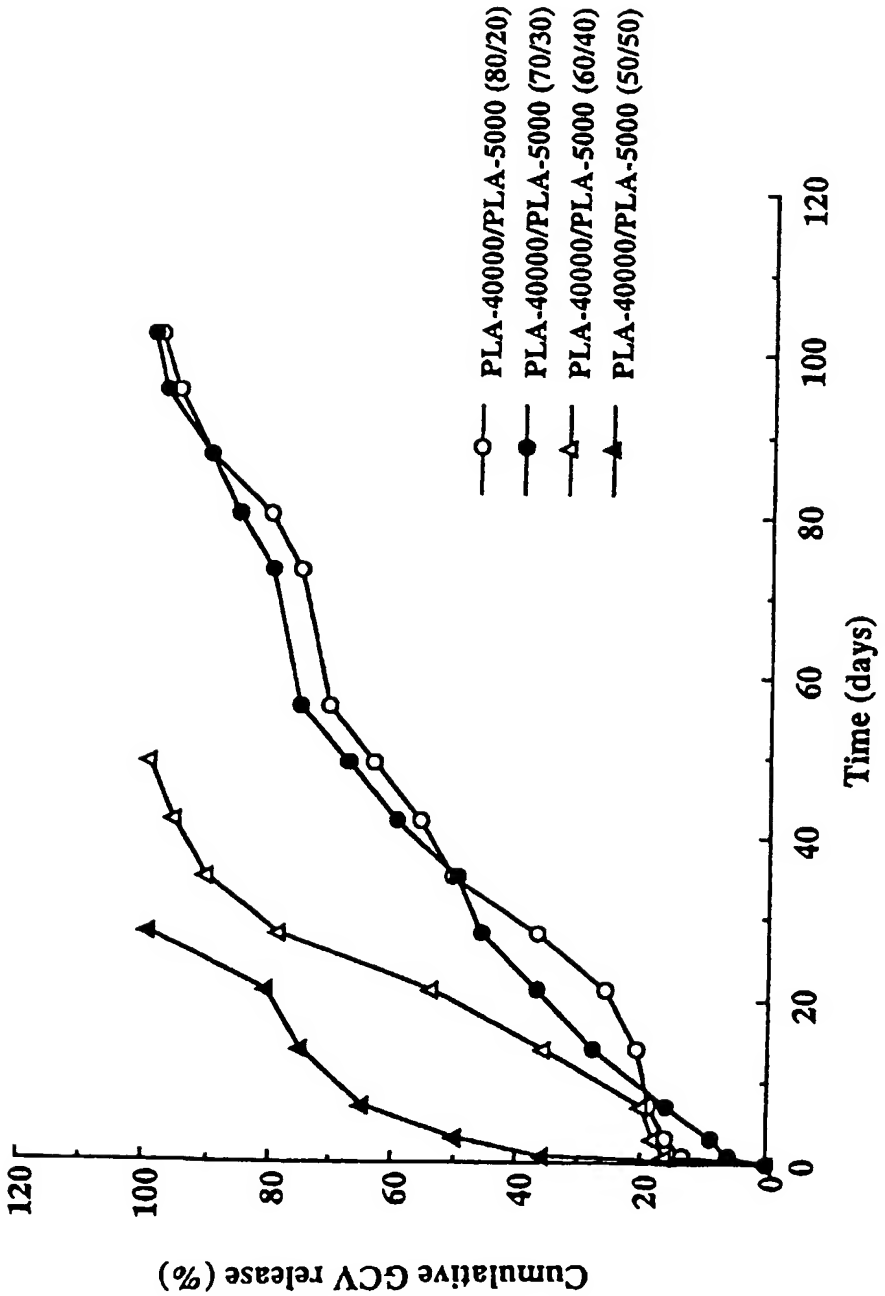

PLA-70000/PLA-20000 (95/5)
PLA-70000/PLA-20000 (80/20)
Cumulative GCV release (%)
Time (days)
0
20
40
60
80
100
120
0
100
200
300
400

Fig.8


PLA-40000/PLA-5000 (80/20)
PLA-40000/PLA-5000 (70/30)
PLA-40000/PLA-5000 (60/40)
PLA-40000/PLA-5000 (50/50)
Cumulative GCV release (%)
Time (days)
0
20
40
60
80
100
120

## INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/02916

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl⁶ A61K47/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl⁶ A61K47/30

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | JP, 6-312943, A (Santen Pharmaceutical Co., Ltd.), 8 November, 1994 (08. 11. 94) (Family: none) | 1-9 |
| A | JP, 5-17370, A (Senju Pharmaceutical Co., Ltd.), 26 January, 1993 (26. 01. 93) (Family: none) | 1-9 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 August, 1998 (24. 08. 98) | 1 September, 1998 (01. 09. 98) |
| Name and mailing address of the ISA/ Japanese Patent Office | Authorized officer |
| Facsimile No. | Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1992)